THE REGULATION OF NORMAL BREATHING.

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It has recently been shown[1] that under normal conditions, which may vary very widely, the breathing is so regulated by the respiratory centre as to maintain a constant, or nearly constant, level in the partial pressure of CO_2 in the alveolar air, and therefore also in the arterial blood. The centre is extremely sensitive to the slightest increase or diminution in CO_2-pressure. From experiments in which there was an added percentage of CO_2 in the inspired air Haldane and Priestley found that a rise of as little as 0·2 % of CO_2 in the alveolar air, corresponding to an increase of 1·4 mm. in the CO_2-pressure, was sufficient to increase the alveolar ventilation by 100 %.

The respiratory centre must evidently be regarded as a very sensitive governor of the CO_2-pressure in its own substance, and indirectly in the arterial blood and alveolar air. We may compare its action to that of the governor of an engine driven by steam or water, if we bear in mind that the respiratory centre governs CO_2-pressure, whereas the governor of the engine controls its rate of revolution.

It is well known to engineers that something more than a sensitive governor is needed in order to produce practical constancy in the rate of revolution of an engine—for instance a steam-engine or water-turbine driving a dynamo at a constant rate, so as to obtain a constant voltage in spite of very variable amounts of current being produced by the dynamo. The governor must not merely be sensitive, but it must not cause or permit temporary irregularities, nor must it "hunt," *i.e.* cause periodic variations in speed owing to its alternate excessive and

[1] Haldane and Priestley. This *Journal*, xxxii. p. 225. 1905.

insufficient action. To prevent these irregularities a heavy flywheel, or some equivalent arrangement, is needed.

The breathing has to vary rapidly and within wide limits in order to meet corresponding variations in the respiratory exchange owing to varying amounts of muscular work. There are also many minor voluntary or involuntary disturbances in normal and regular breathing. These conditions have to be met by the governing action of the respiratory centre. Under ordinary conditions the action of the centre appears to be both smooth and certain; but it has been shown in the previous paper how easily periodic breathing, which is clearly analogous to the "hunting" of a governor, may be produced under unusual conditions. Such factors as the production of lactic acid may also disturb the normal regulation of breathing, and produce effects of the kind recently described by Boycott, Haldane, Poulton, and Ogier Ward[1]. The conditions which determine the smoothness of the governing action of the respiratory centre, and the manner in which it reacts to muscular work, have not hitherto been at all completely investigated, and form the subject of the present paper.

The experiments have, for obvious reasons, been made on Man. In order to study the governing action of the respiratory centre we have introduced various disturbances, including muscular work; and taking these one by one we shall describe the manner in which the centre responds to them.

Holding the breath. If the breath is voluntarily held for a short time, marked compensatory hyperpnœa follows, both the depth and frequency of respiration being increased, as shown in Fig. 1, which represents a tracing given by a modified Marey stethograph. Table I shows the gas-pressures in samples of alveolar air taken at different periods after the subject (C. G. D.) had held his breath for 30 seconds.

On examining Table I and the corresponding tracing it will be seen at once that although the alveolar CO_2-pressure rose to far above normal while the breath was held, yet during the subsequent hyperpnœa the CO_2-pressure fell to considerably below normal, and only gradually rose to normal again during the next two or three minutes, as the hyperpnœa gradually subsided. It will also be noticed that in spite of the secondary fall below normal in the alveolar CO_2-pressure, the activity of the centre did not fall below normal, but gradually and smoothly returned to normal, without any of the oscillations which an imperfectly acting governor would show.

[1] This *Journal*, XXXVII. pp. 355, 378, 390.

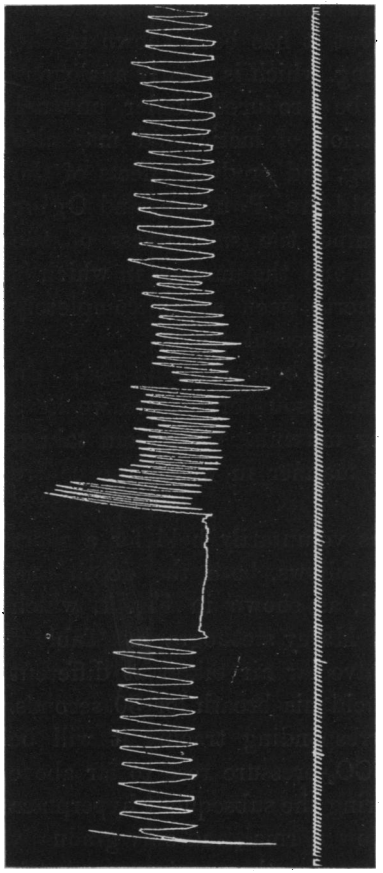

Fig. 1. Stethograph tracing. Breath held 30 seconds. At 20th expiration after breathing began again a sample of alveolar air was taken. $CO_2 = 4{\cdot}77\ \%$.

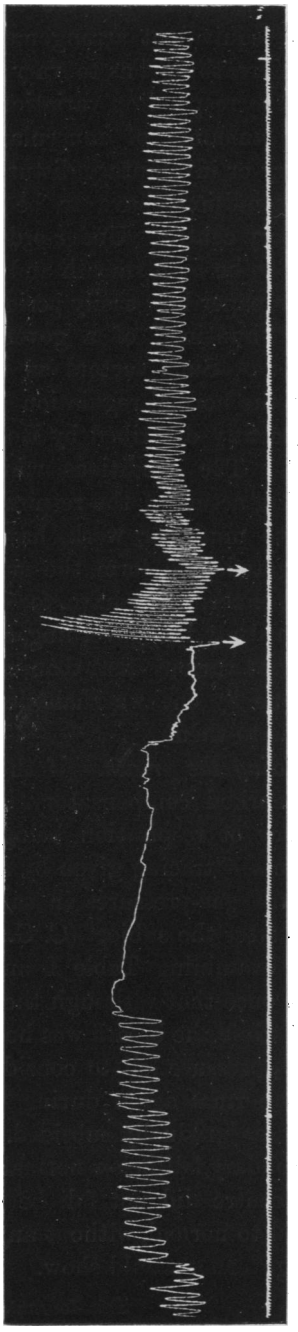

Fig. 2. Stethograph tracing. Breath held 130 seconds after six normal breaths of oxygen. At first arrow alveolar $CO_2 = 8{\cdot}66\ \%$, $O_2 = 38{\cdot}22\ \%$; at second arrow $CO_2 = 4{\cdot}65\ \%$.

If the centre responded rapidly and completely to every change in the alveolar CO_2-pressure it seems clear that there would be great hyperpnœa for a few seconds after the holding of the breath was discontinued, as blood abnormally charged with CO_2 would still be passing through the centre. But directly afterwards apnœa would be produced, on account of the abnormally low alveolar CO_2-pressure, and consequent low CO_2-pressure in the arterial blood. The apnœa would, in turn, be followed by hyperpnœa, and again by apnœa, as in Cheyne-Stokes respiration. The centre would, in fact, "hunt," like a badly acting governor.

TABLE I.

	Pressure in mm. of Hg in alveolar air	
	CO_2	O_2
At end of period of holding breath for 30″ ...	49·2	62·6
At fifth expiration	26·0	—
	30·0	—
	31·4	112
At eighth expiration	32·6	—
At ninth expiration	31·5	—
At twelfth expiration	32·0	—
At twentieth expiration	33·8	—
At thirtieth expiration	37·0	—
At fortieth expiration	38·8	—
At fifth expiration after holding for 40″	28·4	117
At eighth ,, ,, ,, ...	29·4	—
At end of holding breath for 130″ after oxygen ...	61·9	274
At sixth expiration	24·8	—
At twentieth expiration	33·3	—
At fortieth expiration	31·2	—
Normal average	39·75	105

The actual facts point to the following explanation. During the holding of the breath the centre itself, and not merely the blood, becomes gradually charged with an accumulation of CO_2, in combination, doubtless, with alkali for the most part. After the breathing is allowed to recommence it takes some time for this accumulated CO_2 to be washed out, and consequently the hyperpnœa only gradually subsides. As the washing out proceeds the hyperpnœa becomes less and less, and the CO_2-pressure in the alveolar air and arterial blood also rises nearer and nearer to the normal, so that the breathing returns quite gradually and smoothly to its normal amount. The storage of CO_2 in the

respiratory centre appears, therefore, to have the same influence on its action as a heavy fly-wheel has on the action of an engine with a sensitive governor; and irregular or periodic breathing is thus prevented.

The matter is, however, not quite so simple as has just been assumed: for Hill and Flack[1] have recently shown that when the breath is held, want of oxygen, as well as excess of CO_2, acts on the respiratory centre. They found that if the lungs are filled with oxygen before the breath is held, the effect of the oxygen is to prolong greatly the time during which the breath can be voluntarily held, and to increase correspondingly the alveolar CO_2-percentage. This result, which we have confirmed, is at first sight very anomalous, since it is known that during normal breathing the alveolar oxygen-pressure may vary within wide limits upwards or downwards without the breathing being affected; and an examination of their and our own figures shows that when no oxygen had been added the alveolar oxygen-pressure often did not fall below these limits. In their experiments they appear to have employed oxygen-percentages greatly in excess of the normal alveolar oxygen-percentage. As it did not seem clear from their results how great an excess of oxygen was needed, or how this excess acted, we have repeated these experiments with this difference, that by taking a variable number of breaths (from a single normal breath to two minutes' normal breathing) from a bag of oxygen fitted with inspiratory and expiratory valves, it was possible to secure wide variations in the alveolar oxygen-pressure at the point where the subject was no longer able to resist the desire to breathe. The results of a series of experiments on C. G. D. are collected in Table II in the order in which they were made.

It will be seen from Table II that as the alveolar oxygen-pressure at the breaking-point rose there was a prolongation of the time during which the breath could be held, and a progressive rise in the alveolar CO_2-pressure, but that this beneficial action was only shown in the case of oxygen-pressures below about 120 mm. Above this point excess of oxygen was without influence on the ability of the subject to withstand a rising CO_2-pressure. In other words, deficiency of oxygen, or the development of lactic acid which accompanies it, began to assist in exciting the centre when the alveolar oxygen-pressure fell below about 120 mm., whereas during normal breathing the oxygen-pressure has to fall to about 60 mm. to cause a similar effect.

[1] This *Journal*, xxxvii. p. 77. 1908.

This at first sight anomalous fact is evidently due to a cause which has been discussed in detail in the preceding paper. The slight circulatory block produced by suspending the breathing is sufficient to diminish appreciably the oxygen supply to the respiratory centre. In consequence of this, lactic acid begins to be formed in the centre, and the threshold exciting pressure of CO_2 is correspondingly lowered, if the alveolar oxygen falls below about 120 mm., whereas under normal conditions a fall to about 60 mm. is needed in order to produce the same effect.

TABLE II.

Duration of period of holding breath up to breaking-point in seconds	Pressure in mm. of Hg in alveolar air		
	CO_2	O_2	
40	—	—	Without preparation.
48	—	—	After three fairly large breaths of air.
65	—	—	,, ,, ,, ,, O_2.
55	—	—	,, ,, ,, ,, air.
75	—	—	,, ,, ,, ,, O_2
50	52·6	96·2	With oxygen.
60	53·1	78·2	,, ,,
57	53·3	86·5	,, ,,
80	55·4	119·6	,, ,,
80	58·1	200·1	,, ,,
65	54·7	111·6	,, ,,
80	57·6	120·4	,, ,,
35	51·2	59·8	Without oxygen.
35	49·2	61·2	,, ,,
80	58·0	103·8	With oxygen.
95	58·6	116·9	,, ,,
120	61·8	175·7	,, ,,
110	62·0	110·8	,, ,,
108	61·2	117·6	,, ,,
45	52·6	57·1	Without oxygen.
105	59·5	89·0	With oxygen.
133	67·3	466·0	,, ,,
150	64·0	436·3	,, ,,
110	60·8	101·2	,, ,,
105	66·0	115·7	,, ,,
	39·75	105·0	Average normal alveolar air.

If this explanation is correct we should expect to find that where there is no hindrance to the breathing want of oxygen would produce as little effect in presence of accumulating CO_2 as when no excess of CO_2 is present. In order to test this point we used the large 50 litre cylinder and quantitative recording arrangement described in the

preceding paper. At the beginning of each experiment the cylinder was filled with a mixture of oxygen and nitrogen. This mixture was then breathed for 10 minutes, at the end of which time there was always great hyperpnœa, and the percentage of CO_2 had risen to about 6·0 to 6·3, with the alveolar CO_2 about 1 % higher. The records showed that it made no difference at all to the hyperpnœa whether the cylinder was filled with air or a mixture richer in oxygen; and that when mixtures poorer in oxygen than air were used it made no difference whatever unless the initial oxygen-percentage in the cylinder was under 15. The following Table shows the initial and final percentages of oxygen and CO_2 in the cylinder. Only in the fifth experiment, where the alveolar oxygen-percentage must have fallen to less than 50 mm., could even a slight increase in the hyperpnœa be detected. Figs. 3 and 4 show the last two records.

TABLE III.

		Air in cylinder at beginning	Air in cylinder at end
Exp. 1	O_2	20·93	13·66
	CO_2	0·03	6·28
Exp. 2	O_2	—	26·04
	CO_2	0·0	6·31
Exp. 3	O_2	17·76	11·82
	CO_2	0·40	5·92
Exp. 4	O_2	15·13	9·11
	CO_2	0·34	6·12
Exp. 5	O_2	12·96	7·79
	CO_2	0·25	6·30
Exp. 6	O_2	20·93	13·50
	CO_2	0·03	6·01

These experiments confirm the conclusion reached by Haldane and Lorrain Smith in 1892[1]. Hill and Flack[2], and Pembrey and Cook[3], quote evidence that want of oxygen may contribute to the dyspnœa when the subject breathes into a very small closed space. In all these experiments, however, the *alveolar* oxygen was almost certainly lower than its exciting value in the absence of excess of CO_2. Hill and Flack conclude that the diminished circulation when the breath is held

[1] *Journ. of Pathol. and Bacteriol.* I. p. 168. 1892.
[2] This *Journal*, XXXVII. p. 77. 1908.
[3] *Ibid.* XXXVII. *Proc. Physiol. Soc.* p. xli.

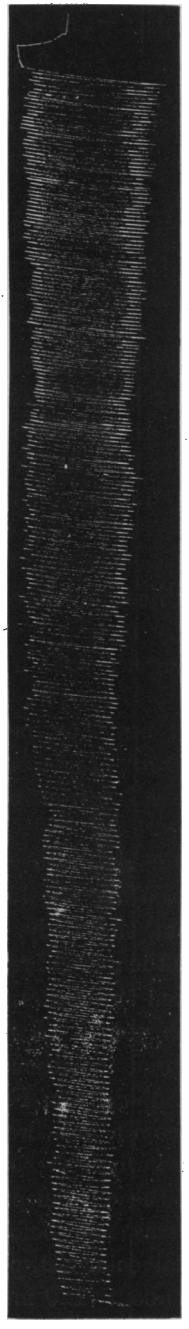

Fig. 3. Quantitative record of breathing for 10 minutes. Air at beginning was pure. Air at end contained 13·50 % of O_2 and 6·01 % of CO_2.

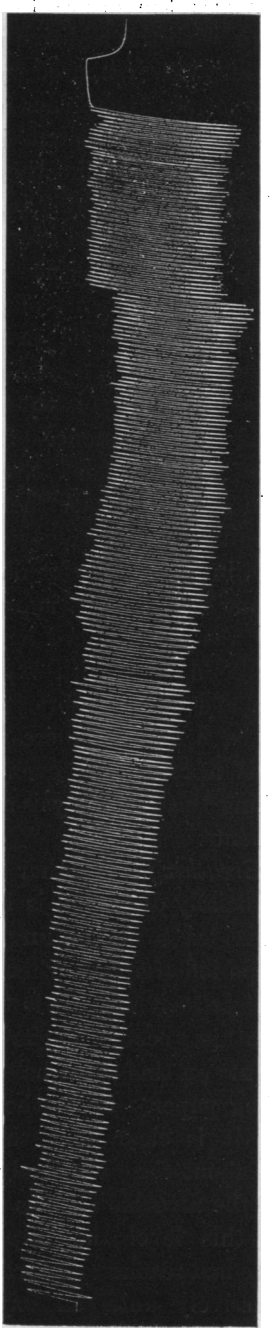

Fig. 4. Quantitative record of breathing for 10 minutes. Air at beginning contained 12·96 % of O_2, and 0·25 % of CO_2. At end 7·79 % of O_2 and 6·30 % of CO_2.

greatly increases the desire to breathe. In this conclusion we can confirm them, with the addition that it is by producing lack of oxygen that the diminished circulation acts, and that apart from the diminished circulation want of oxygen does not affect the result.

The concluding experiments in Table I, of which one of the records is given in Fig. II, show that the "fly wheel" action, due to the slowness with which CO_2 accumulates in, or is washed out of, the respiratory centre, is still more marked when want of oxygen is eliminated. This fact is readily intelligible, since a larger excess of CO_2 will accumulate in the centre in consequence of the breath being held longer, and this excess will take longer to be washed out.

The behaviour of the centre when excited in consequence of excess of CO_2 in the alveolar air is thus in marked contrast with its behaviour when excited in consequence of want of oxygen. In the former case there is no "hunting" of the centre when normal air is again breathed: in the latter case there is pronounced "hunting," as shown in the preceding paper.

The data in Table II were obtained from successive experiments on three different days, and it is evident that the subject improved with practice, as was also noticed by Hill and Flack. A very noticeable fact, also, in connection with experiments on holding the breath is that towards the end of the effort it is very difficult to keep still. There appears to be a general increase of excitability; and any muscular movement is a relief. It even required considerable self-control to avoid breaking the gas analysis apparatus, which stood in front of us in the experiments.

Forced Breathing. Another method by which the respiratory centre may be artificially disturbed is by voluntarily ventilating the lungs to excess. This leads to washing out of CO_2 from the body, and a consequent period of apnœa when the subject ceases the forced breathing. The point of present interest is the manner in which the resumption of natural breathing occurs at the end of the apnœic pause. A number of experiments on this point have already been quoted and discussed in the preceding paper. From the results shown graphically in Fig. 3 of that paper it is clear that the stimulus to recommence breathing occurred at about the normal alveolar CO_2-pressure when the oxygen-pressure of the alveolar air was about 42 mm. If the oxygen-pressure was below this level the impulse to breathe was felt before the CO_2-pressure had reached its normal: if above, the alveolar CO_2-pressure rose progressively until an oxygen-pressure of about 120 mm. was

reached; but above this level it did not matter what the oxygen-pressure was.

The explanation we offer is that after forced breathing, and the consequent washing out of CO_2 from the centre, a considerable time must elapse before the gradually accumulating CO_2 can saturate the centre to the threshold exciting pressure. So soon as this point is reached the breathing starts quietly and evenly if want of oxygen has been eliminated. If, however, only ordinary air is inhaled during the forced breathing, the effects of want of oxygen show themselves, and the breathing begins before the CO_2-pressure in the centre has reached the normal exciting value. As a consequence, the supply of oxygen to the lungs and blood at once removes the stimulus to breathing, and the centre at first overshoots the mark, and may continue for several minutes to oscillate between hyperpnœa and apnœa, as shown in the preceding paper.

Breathing Air containing Excess of CO_2. In order to study the reaction of the centre when it is suddenly disturbed by excess of CO_2 in the inspired air, the subject was allowed to breathe through a mouthpiece and valves so arranged that either pure air or air from a large bag could be breathed through an inspiratory tube, while a sample of alveolar air could be collected from an expiratory tube returning to the bag. The bag was filled with respired air containing a known percentage of CO_2, a little oxygen being also added to avoid any excessive deficiency of oxygen.

In the first pair of experiments the bag contained 4·74 % of CO_2 and 16·52 % of O_2 (sample taken between the first and second alveolar samples). A sample of alveolar air taken at the 5th expiration, as the hyperpnœa was beginning, contained 6·82 % of CO_2 and 11·90 % of O_2, while a sample at the 30th respiration, when the hyperpnœa was fully developed, contained 6·56 % of CO_2 and 13·62 % of O_2. The lower oxygen percentage in the first sample was evidently due to the delay in the reaction of the centre to the increased percentage of CO_2. The CO_2-percentage in the first sample is only, however, very slightly higher than in the second, the reason evidently being that the giving off of CO_2 by the venous blood was hindered. But for this the CO_2-percentage would doubtless have been much higher in the first sample.

Further experiments were made with a mixture which contained 7·18 % of CO_2 and 17·79 of O_2 at the beginning of the experiments, and 7·12 % of CO_2 and 16·76 % of O_2 at the end. At the 6th and 10th

expirations, while the hyperpnœa was developing, the alveolar air contained 7·17 and 7·46 % of CO_2, with 12·85 and 12·72 % of O_2. At the 30th expiration, when the hyperpnœa had for some time been fully developed, the alveolar air contained 7·42 % of CO_2 and 15·40 % of O_2. The result was thus very similar to that of the previous experiment, but so completely was the giving off of CO_2 hindered that the air of the bag actually contained somewhat less CO_2 at the end than at the beginning, although the oxygen had fallen by 1·03 %.

The graphic records showed that the hyperpnœa developed smoothly and gradually after the first three breaths. There was no indication of initial hunting, such as occurs when the hyperpnœa is produced by breathing through a long tube. In the latter case the hyperpnœa suddenly and greatly reduces the alveolar CO_2-pressure, whereas when respired air is breathed from the bag there is at most only a slight and gradual reduction. As there was no permanent "hunting" with the bag experiments, the influence of want of oxygen was nil, in accordance with the explanation given in the preceding paper.

When normal air was breathed again after breathing the mixture rich in CO_2 the hyperpnœa passed off evenly and gradually, in the manner shown in Figs. 1 and 2. This is in marked contrast to the periodic breathing produced after hyperpnœa caused by want of oxygen. The normal stimulus of excess of CO_2, whether in its development or in its disappearance, causes no "hunting," while the abnormal stimulus of oxygen want readily produces it.

Muscular Work. The effects of muscular work on the respiratory centre are considerably more complex and difficult to analyse than those of any of the experimental disturbances hitherto considered. It was shown by Haldane and Priestley[1] that during moderate muscular work the breathing is increased in such a way as to keep the alveolar CO_2-pressure from rising more than a little above normal, and that there is every reason to believe that the hyperpnœa of such work is due simply to slight excess of CO_2-pressure in the arterial blood, and consequently also in the respiratory centre. These experiments were made during work on a stationary tricycle provided with a brake, by means of which the amount of work could be varied at will, and they did not study the effects of excessive work. In order to further elucidate the reaction of the respiratory centre to muscular work we have made a variety of further experiments.

[1] This *Journal*, xxxii. p. 225. 1905.

The first series was made with the object of observing the changes in the alveolar CO_2-pressure during the period immediately following a sudden and considerable exertion. For this purpose we had chosen the exertion of running quickly up three flights of stairs (40 feet in all), at the top of which the apparatus for obtaining and analysing the alveolar air was arranged. In successive experiments samples of the alveolar air were taken after different intervals of time had elapsed after reaching the top. We soon found, however, that the results were much influenced by the after-effects of each experiment, and were thus not comparable. The following Table shows the effects on the alveolar CO_2-pressure of three successive experiments, in which the subject (C. G. D.) ran quickly up, down, and again up the stairs in about 45 seconds.

TABLE IV.

Time after stop	Pressure of CO_2 in alveolar air in mm. of Hg	
10″	49·2	
3′ 0	35·4	Sample at end of inspiration.
6′ 30″	35·3	,, ,, ,,
12′ 30″	35·8	,, ,, expiration.
10″	38·9	
3′ 0″	33·7	Sample at end of inspiration.
6′ 30″	34·4	,, ,, ,,
10″	36·9	
3′ 0″	34·4	Sample at end of inspiration.
8′ 30″	32·4	,, ,, ,,
18′ 30″	33·7	,, ,, ,,
24′ 0″	36·2	,, ,, expiration.
	39·0	Normal alveolar air at end of inspiration, average.

It will be seen that the immediate effect of the exertion was to raise the alveolar CO_2-pressure (by about 10 mm. in the first experiment), but that in successive experiments this rise was less, and that the rise was followed by a fall, which reached its maximum about 10 minutes after the exertion, and was greater after each successive exertion[1].

[1] It will be noticed that although the fall was somewhat greater in the third than the second experiment there are indications that a balance had nearly been struck between formation and disappearance of lactic acid. All the phenomena connected with what we believe to be the production of lactic acid in consequence of oxygen want suggest that a balance between formation and destruction of lactic acid establishes itself for each degree of oxygen want.

This secondary fall was invariably observed after any considerable exertion, and lasted for far too long a time to be attributable to the fall in CO_2-pressure in the respiratory centre lagging behind the fall in the alveolar CO_2-pressure. The following experiments, in several of which Mr F. A. Hampton kindly acted as subject, may be quoted in illustration.

It seems clear from these experiments that any unusual exertion lowers for some time the alveolar CO_2-pressure. The effect is similar to that following exposure to want of oxygen, as described by Boycott, Haldane, and Ogier Ward[1], and we have little doubt that it is due to the same cause, namely the development of lactic acid within the body. It seems quite justifiable to assume that during any excessive exertion the supply of arterial blood to the muscles in use becomes for the time inadequate, so that they suffer from want of oxygen and consequently produce lactic acid. This acid enters the blood and helps the CO_2 to excite the respiratory centre, so that the alveolar CO_2-pressure becomes lower than would otherwise be the case. The lactic acid remains for a considerable time in the blood after the immediate effects of the exertion have passed off, and consequently the alveolar CO_2-pressure falls to below normal, and may remain abnormally low for about an hour after the exertion, as shown in some of the experiments in Table V.

In the first series of experiments (Table IV) the rate at which the work was done can easily be calculated. The work consisted in running quickly up 40 feet of stairs, this being done in 12 seconds. Thus the external work done was $150 \times 40 = 6000$ foot-pounds in 12 seconds, or at the rate of about 30,000 foot-pounds, or 4000 kilogrammeters per minute. This is far in excess of what can by any possibility be kept up by a man. With a mechanical efficiency of about a third such work would imply a metabolism at a rate of about 27 Calories per minute, as against the normal resting metabolism of about $1\frac{1}{2}$ Calories per minute. It seems inevitable that any such rate of exertion must bring about a condition of muscular asphyxia, and a rapid formation of lactic acid in the muscles is exactly what might be expected.

It is interesting to compare the results of sudden and excessive muscular exertion with those of the long cross-country run of about 8 miles in 57 minutes without a stop. It will be seen from Table V that after this prolonged exertion the alveolar CO_2-pressure only fell to about 10 % below normal—no more than after running twice up the laboratory stairs! In the cross-country run the rate of exertion

[1] This *Journal*, xxxvii. pp. 355, 378. 1908.

TABLE V.

Alveolar CO_2-pressure in mm. of Hg

	End of inspiration	End of expiration	Mean
Average for C. G. D.	39·0	40·6	39·8
Just before running	39·6	40·7	40·2
10″ after running 600 yards in 2′ 10″ ...	42·2	—	—
7′ afterwards	35·5	—	—
12′ ,, ...	36·2	—	—
17′ ,, ...	34·9	—	—
47′ ,, ...	38·6	38·4	38·5
70′ ,, ...	39·6	—	—
10″ after running 110 yards as fast as possible just after last experiment	52·3	—	—
5′ afterwards	37·5	—	—
Normal before running, C. G. D. ...	38·2	40·8	39·5
10″ after running 300 yards in 52″ ...	45·7	—	—
10′ afterwards	35·6	—	—
15′ ,, ...	33·0	—	—
25′ ,, ...	33·8	34·9	34·1
43′ ,, ...	37·8	38·4	38·1
60′ ,, ...	38·4	39·7	39·1
Average normal for J. S. H.	—	—	41·1
15′ after thrice running 200 yards quickly	32·4	—	—
25′ ,, ,, ,, ,,	34·4	35·6	35·0
Average normal for F. A. H.	45·8	46·6	46·3 [1]
Just before running	46·9	45·9	46·4
Just after running ¼ mile in 1′ 36″ ...	58·0	—	—
5′ afterwards. Hyperpnœa gone ...	41·0	42·8	41·9
15′ ,, ...	39·0	42·8	40·9
26′ ,, ...	42·9	—	—
Just after running for 7′ more	46·4	—	—
Just after running a further 7′ ...	38·4	—	—
9′ afterwards	37·4	36·6	37·0
30′ ,, ...	39·8	43·0	41·4
90′ ,, ...	44·9	45·9	45·4
F. A. H. Just after running ¼ mile ...	55·4	—	—
15′ later	39·3	—	—
30′ ,, ...	41·3	45·7	43·5
Just after another ¼ mile in 80″ ...	50·6	—	—
15′ later	37·7	36·7	37·4
F. A. H. Before running	44·4	45·1	44·8
Just after cross-country run of 57′ without a stop	51·0	—	—
10′ afterwards (temp. of urine = 99° F.) ...	40·0	—	—
22′ ,, ...	39·6	40·2	39·9
60′ ,, ...	44·2	44·4	44·3
F. A. H. Just after running ¾ mile in 4′ 0″	42·3	—	—
15′ afterwards	36·8	37·4	37·1
50′ ,, ...	43·7	44·8	44·3

[1] The average normal alveolar CO_2-pressure of F. A. H. is the highest hitherto recorded. It may also be of interest to mention that in the case of Dr Priestley, who in 1903–04 gave the very high value of 44·5 mm. we found 45·9 mm. in 1909 as the result of a double determination. In J. S. H. and C. G. D. the alveolar CO_2-pressure has also remained nearly steady since 1904.

was evidently within the power of the runner to keep it up over a long period. He was at the time in training and accustomed to long cross-country runs.

A further series of experiments was made in which the subject inhaled oxygen, on two occasions just before beginning the same exertion as in the experiments in Table IV, and on a third occasion for two minutes following the stop. In neither case did the oxygen prevent the secondary fall in the alveolar CO_2-pressure. The results are given in Table VI. The experiments were again consecutive, and all samples with one exception were taken at the end of inspiration.

TABLE VI.

Time after stop	Pressure of CO_2 in alveolar air in mm. of Hg	
10″	47·0	Seven breaths of O_2 before start.
3′ 30″	35·2	
7′ 30″	37·7	
12′ 0″	35·7	
16′ 30″	35·3	
22′ 30″	36·9	Sample at end of expiration.
10″	41·4	Ten breaths of O_2 before start.
4′ 0″	36·1	
8′ 0″	35·4	
17′ 30″	38·3	
23′ 30″	37·8	
1′ 0″	39·2	Oxygen breathed for 2 minutes after first sample taken.
5′ 30″	34·0	
10′ 0″	34·6	
	39·0	Normal for C. G. D. at end of inspiration.

Lowering of the threshold exciting pressure of CO_2 must have two effects on the breathing. In the first place a greater lung ventilation is required in order to keep the alveolar CO_2-pressure down to about the threshold exciting value with any given discharge of CO_2 from the body. Thus if the threshold exciting pressure of CO_2 is lowered from 40 to 32 mm. the alveolar ventilation will need to be increased in the proportion of 40 to 32, or by 25 %, with a normal discharge of CO_2. During great hyperpnœa from muscular exertion the effect seems to be still more marked. In the first experiment on F. A. H., for instance, the alveolar CO_2-pressure just after the exertion fell from 58·0 mm. in the first observation, to 38·4 in the third, implying an increase of 50 % in the alveolar ventilation per unit of

CO_2 discharged. It seems also pretty certain that but for lactic acid already formed the value of 58·0 in the first observation would have been considerably exceeded; and it is reasonable to conclude that during, and just after, vigorous muscular exertion the blood reaching the respiratory centre contains more lactic acid than soon afterwards, as the proportion coming directly from the active muscles, and therefore highly charged with lactic acid, must be very great during the exertion, whereas later this blood will be thoroughly mixed with the rest of the blood. This assumption explains the fact that the hyperpnœa from muscular exertion seems often out of proportion to the rise in alveolar CO_2-pressure.

A second effect on the breathing must also be produced by the lowering of the threshold exciting value of CO_2: for a removal from the blood and tissues of a considerable amount of preformed CO_2 will be necessitated. Until this redundant CO_2 has been removed the breathing will for the time be much more increased than would otherwise be the case. Haldane and Poulton[1] have shown that a rapid, though comparatively slight, lowering of the threshold exciting pressure of CO_2 explains the excessive hyperpnœa which may be temporarily produced by deficiency of oxygen in the air breathed. A similar effect must result from the rapid fall in threshold CO_2-pressure during excessive muscular work, so that for some time the hyperpnœa will be much greater than would otherwise be the case. A direct indication of this effect is the abnormally high respiratory quotient which exists during excessive muscular work, just as when air very poor in oxygen is breathed. That the respiratory quotient becomes abnormally high is well shown in the experiments of Hill and Flack[2] and of Pembrey and Cook[3] on the alveolar air just after muscular exertion, and has also been observed by Loewy[4] and others. In several of the experiments in Table V the alveolar oxygen percentage was determined, as well as the CO_2, so that the respiratory quotient could be calculated. For instance, just after running $\frac{1}{4}$ mile F. A. H. had a respiratory quotient of 1·10, which had fallen 15 minutes later to ·83; and just after $\frac{3}{4}$ mile he had a quotient of 1·04, which had fallen 15 minutes later to ·72. On the other hand, just after the long cross-country run

[1] This *Journal*, XXXVII. p. 390. 1908.

[2] *Ibid.* XXXVI. *Proc. Physiol. Soc.* p. xl. 1907.

[3] *Ibid.* XXXVII. *Proc. Physiol. Soc.* p. lxvii. 1908.

[4] *Pflüger's Archiv.* XLIX. p. 405. 1891. Loewy traced the abnormal quotient to deficient oxygen supply to the muscles.

of about 8 miles he had a quotient of only ·87, and ·88 22 minutes later. In this case all the redundant preformed CO_2 had been discharged before the end of the run, so that the quotient was normal. There was also no excessive respiratory distress and the alveolar CO_2-pressure (51 mm.) was comparatively high. The lactic acid production was evidently slight, as already remarked, and (probably quite early in the run) a balance had been struck between its production and destruction or excretion.

It will also be seen from Table V that even during the great hyperpnœa of excessive muscular work the alveolar CO_2-pressure may actually fall below normal. This is likewise well shown in the experiments, just quoted, of Hill and Flack.

We have also tried the effect of removing, by forced breathing, some of the preformed CO_2 from the body just before muscular exertion. After the third experiment in Table V, the subject (C. G. D.) breathed moderately forcibly for one minute, and then again ran 300 yards. The hyperpnœa and distress at the end of the run were remarkably lessened, although the alveolar CO_2-pressure afterwards fell to exactly the same level as in the previous experiments, showing that the forced breathing had not in any way prevented the formation of lactic acid. On a subsequent occasion three runs of 200 yards were made by both of us, the distance being covered in each of the three runs in the same time. The first and last runs were made after forced breathing for one minute: the second without any previous preparation. An interval of 20 minutes was allowed between the runs. There was the same remarkable relief from distress at the end of those runs which were made after forced breathing. The alveolar CO_2-pressure of J. S. H. was 32·4 mm. (inspiratory value) 15 minutes after the last run, and 35 mm. (mean value) 10 minutes later. For C. G. D. the inspiratory value was 36·1 mm. 16 minutes after the last run.

It has been brought to our notice that it is the custom of good boxers to breathe deeply during the intervals between the rounds for a short time just before the call of "time."

Hill and Flack[1] have recently called attention to beneficial results attributed to inhaling oxygen before and after muscular exertion. In connection with conclusions as to such effects it seems necessary to eliminate carefully any effects produced by extra deep inhalations washing out CO_2 from the body.

[1] *Brit. Med. Journ.* p. 499, Aug. 22, 1908; and this *Journal*, xxxviii. *Proc. Physiol. Soc.* p. xxviii. 1909.

The fact that preliminary forced breathing lessens the hyperpnœa produced by muscular work affords striking confirmation to the conclusion that the hyperpnœa is due to the pressure of CO_2 being considerably above the existing threshold exciting value.

In the forms of muscular work which have so far been investigated the exertion has been excessive. We have also investigated more moderate and accustomed forms of exercise. Table VII shows results obtained after walking. The figures given are the mean values for samples of alveolar air obtained at the end of inspiration and of expiration.

TABLE VII.

		Alveolar CO_2-pressure in mm. Hg
C. G. D.	Just after walking 600 yards at 5 miles an hour ...	45·4
	10′ later	39·6
	Just after walking 600 yards at 6 miles an hour ...	44·3
	10′ later	37·4
	15′ ,, ...	36·8
	Normal alveolar air, average	39·75
J. S. H.	5′ after walking 600 yards at 4 miles an hour ...	39·9
	6′ after again walking 600 yards at 4 miles an hour	41·4
	Just after walking 700 yards at 4 miles an hour ...	41·8
	15′ later	40·6
	Just after walking 600 yards at 5 miles an hour ...	39·3
	10′ later	39·0
	15′ ,, ...	39·0
	7′ after trotting 600 yards at 5 miles an hour ...	37·9
	13′ later	39·3
	Normal alveolar air, average	41·1

It will be seen that no secondary fall in alveolar CO_2-pressure followed the moderate work. Increasing the pace in the case of C. G. D., however, from 5 to 6 miles an hour, caused a distinct lowering of the alveolar CO_2-pressure, which lasted some time, so the faster pace seems to have induced the formation of lactic acid. The same alteration occurred to a slight extent when J. S. H. walked at 5 miles an hour: also when he trotted at the same pace.

Quite moderate work (about 2500 foot-pounds per minute) on a tricycle ergometer similar to that used by Haldane and Priestley was not found to lower the alveolar CO_2-pressure after cessation of the work. The figures are given in Table VIII, and confirm Haldane and Priestley's original results.

TABLE VIII.

		Pressure of CO_2 in alveolar air in mm. of Hg
J. S. H.	Samples after 3′ and 3¾′ work ...	39·6
	Samples 15′ later	41·9
	Samples after 3′ and 3½′ work ...	40·1
	Samples 10′ later	41·6
	Normal alveolar air, average ...	41·1
C. G. D.	Samples after 3′ and 3½′ work ...	47·5
	Samples some minutes later ...	40·8
	Normal alveolar air, average ...	39·75

Geppert and Zuntz[1] tetanised the hind limbs of a dog, and found that during the hyperpnœa induced by this, and for some time after the cessation of the stimulus, the percentage of CO_2 in the expired air fell, while that of oxygen rose. The percentage of CO_2 in the blood also fell greatly, while that of oxygen remained constant. A similar, but less marked, effect was observed when the animal performed the severe muscular work of dragging a heavy cart through the streets. Seeing that the CO_2-percentage fell the authors erroneously discounted the paramount influence of CO_2 in producing the hyperpnœa, and concluded that it was caused solely by abnormal metabolic products (such as lactic acid) produced in the muscles.

On the other hand Haldane and Priestley concluded that the hyperpnœa is due solely to an absolute rise of CO_2-pressure in the respiratory centre, and pointed out that in the experiments of Geppert and Zuntz the CO_2-carrying power of the blood was probably reduced greatly in consequence of lactic acid formation due to the abnormal conditions under which the muscular work was performed. It might thus be the case that even although the alveolar CO_2-pressure was lower during the muscular work, the CO_2-pressure in the centre was higher. The experiments of Loewy[2] and of Beddard, Pembrey, and Spriggs[3] indicate that a moderate decrease in the alkalinity of the blood has much less effect on its CO_2-carrying power than was formerly supposed, so that the great diminution in the amount of CO_2 in the blood in consequence of acid poisoning, excessive muscular work, &c. must be attributed mainly to increased ventilation of the lungs, due to the acid products helping to excite the respiratory centre.

[1] *Pflüger's Archiv.* XLII. p. 189. 1888.

[2] *Arch. f.* (*Anat. u.*) *Physiologie*, p. 81. 1901.

[3] This *Journal*, XXXI. *Proc. Physiol. Soc.* p. xliv. 1904.

We conclude, therefore, that during and after excessive muscular work lactic acid (and possibly other abnormal products of metabolism) play a distinct part in helping to excite the respiratory centre, although during moderate work excess of CO_2 seems to be the sole stimulus. The part played by the lactic acid ought, probably, to be regarded as a pathological rather than a physiological phenomenon. It adds a certain percentage to the lung ventilation without, apparently, thereby causing anything but disadvantage to the organism, owing to the extra distress produced: for apparently the extra hyperpnœa does not tend to remove the lactic acid, which remains in the blood, and exercises its effect on the respiratory centre long after the exertion and any noticeable hyperpnœa from it have ceased.

After the commencement of a muscular exertion some time elapses before the hyperpnœa developes. It increases gradually, and passes off still more gradually, and quite evenly, as might be expected in view of experiments already quoted. We have made a few experiments on this subject, but consider it hardly worth while to quote them in detail here.

Summary.

The experiments described in the present paper indicate that the respiratory centre acts under normal conditions smoothly and without oscillations in its activity, the reason being that some time is needed for it to become saturated or desaturated to the existing CO_2-pressure of the blood passing through it. But for this fact the centre would undoubtedly "hunt" like the governor of an engine without a fly-wheel, since there is a delay between any rise or fall in the alveolar CO_2-pressure and the time when the blood saturated to this pressure reaches the centre. The fly-wheel action of the CO_2-capacity of the centre must be further reinforced by the presence of the alveolar air (about 4 litres) in the lungs, since the CO_2-percentage in such a considerable volume of air cannot alter very rapidly. The relatively high, and very variable, CO_2-capacity of the blood and tissues must also act in the same direction.

Under the abnormal conditions where excitation of the centre depends partly or wholly on want of oxygen in the respiratory centre lowering the threshold exciting pressure of CO_2 (see the preceding paper), the fly-wheel action just referred to is absent, since the centre responds promptly and strongly to any sudden fall below a certain

oxygen-pressure in the blood passing through it, and the stimulus is equally promptly removed by a corresponding rise in the oxygen-pressure of the blood. The centre is consequently apt to "hunt," producing periodic or Cheyne-Stokes breathing. The absence of any appreciable store of free oxygen in the centre, and the greater variability of the oxygen percentage of the alveolar air, probably account for the relative promptitude with which want of oxygen acts on the centre; but whatever the explanation may be, there can be no doubt of the fact. It also appears to be at any rate extremely probable that want of oxygen acts by permitting a certain amount of lactic acid to show itself in the centre, and that this acid is promptly destroyed when the oxygen supply again becomes sufficient.

Owing to the unfavourable conditions of circulation when the breathing is suspended or rapidly diminished in depth, the centre is readily affected by want of oxygen. In the long run slower circulation through the centre would increase the CO_2-pressure in it, and not merely diminish the oxygen-pressure; but want of oxygen will be produced much more quickly, owing to the storage capacity of the centre being far less for oxygen than for CO_2.

The hyperpnœa of muscular exertion is due solely to rise of CO_2-pressure in the centre if the work is moderate. When, however, the rate of work is at all excessive, the threshold exciting pressure of CO_2 in the centre is lowered for some time, and this appears to be due to formation of lactic acid in the working muscles, and consequent diminution in alkalinity of the blood. Less CO_2 is thus needed to excite the centre, and the hyperpnœa is correspondingly increased, although the lactic acid by itself, in the proportion actually present, would be quite incapable of exciting the centre. As a further consequence of the lowering of the threshold exciting pressure of CO_2 a large amount of preformed CO_2 has to be removed from the body, so that for the time the respiratory quotient is very high, and the hyperpnœa is increased out of proportion to the increased CO_2-production and lowered threshold exciting pressure of CO_2.